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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,072	03/14/2001	Thomas Koehler	WEH204	6854

7590 12/08/2004

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,072	KOEHLER, THOMAS	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/26/01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed August 30, 2004. Claims 1-34 were previously pending. Applicant amended claims 1 and 5 and added new claims 35-46. Claims 1-46 are pending and will be examined.

2. Applicant's amendments did not overcome any of the rejections presented in the previous office action. The reasons for maintaining the rejections are given in the "Response to Arguments" section below.

Response to Arguments

3. Applicant's arguments filed August 30, 2000 have been fully considered but they are not persuasive.

A) Regarding the rejection of claim 5 under 35 U.S.C. 112, second paragraph, Applicant comments that claim 5 has been amended to obviate the rejection. However, it is still not clear what "producing a thinning sequence out of a calibrated nucleic acid" means.

The rejection is maintained.

B) Regarding interpretation of the terms "standard nucleic acid" and "calibrated nucleic acid" as any nucleic acid, Applicant argues that it is not the case since the standard nucleic acids are nucleic acids of precisely defined concentration, as supposedly defined on page 1, lines 25 to 31. However, lines 25-30 of page 1 contain the following:

" A prerequisite for the quantitative use of all of the mentioned technologies is the availability of suitable synthetic or native nucleic acid standards of a precisely defined concentration, which either are used as external, i.e. amplified in parallel assays, or as internal standards (i.e. so-called competitors amplified simultaneously in the same assay)."

Therefore, this paragraph does not contain a definition of the term "standard nucleic acid", but a description of its properties while in solution. Concentration of nucleic acid is not a property of nucleic acid, but a property of a nucleic acid solution. Further, any nucleic acid can serve a purpose of being used as a standard, therefore, denoting a nucleic acid as a standard is an indication of its intended use, not its structural properties.

Applicant further argues that standard nucleic acid is precisely calibrated to serve as control in amplification reactions. Again, calibration is not performed on a nucleic acid, but on its solution, to determine the concentration of nucleic acid. Therefore, as explained above, standardization or calibration of a nucleic acid concentration is not a property of a nucleic acid, but a property of a nucleic acid solution.

C) Regarding the interpretation of the term "carrier nucleic acid", Applicant argues that carrier nucleic acid exhibits a minimum sequence homology relative to the nucleic acid to be detected, as described on page 2, lines 9-14. This paragraph is not a definition of a carrier nucleic acid, but its description. Further, on page 30 of the Response, Applicant states the following (third paragraph):

> "The term "carrier nucleic acid"' means any synthetic or physiologic DNA or RNA preferably submitted to physical cleavage into smaller debris e.g. by sonication,..."

Therefore, Applicant states that the carrier nucleic acid can be any nucleic acid.

D) Regarding the rejection of claims 1-5 and 29-33 under 35 U.S.C. 102(b) over Day et al., Applicant very lengthy arguments are essentially that Day et al. do not teach standard nucleic acids and that drying conditions employed by Day et al. would lead to lysis of diluted (Applicant uses the term "thinned", which is not usually used in reference to solutions of biomolecules) solutions. However, both the fact that the nucleic acid is to be used as a standard or to be diluted has no

bearing on the actual content of the product of Day et al. which consists of dried nucleic acids adsorbed onto walls of a microplate, which anticipates Applicant's invention.

The rejection is maintained.

E) Regarding the rejection of claims 1, 3, 4, 6, 8, 11, 14, 15, 17, 19, 22, 25, 26, 29, 30, 32 and 33 under 35 U.S.C. 102(b) as anticipated by Klatser et al., Applicant argues that Klatser et al. do not teach standard nucleic acids, calibrated nucleic acids or carrier nucleic acids. As explained above, since any of these terms is interpreted as any nucleic acid, nucleic acids of Klatser et al. anticipate Applicant's invention. Applicant further argues that Klatser et al. teach addition of trehalose in the process of freeze-drying, which Applicant does not claim. It does not matter, since Applicant's claim does not exclude using any other compounds in creating the dried nucleic acid composition. Applicant argues that Klatser et al. teach lyophilization of batches or reagents and not aliquots. First, Applicant did not define what "an aliquot" means, and usually it means a portion of an original solution. Klatser et al. teach aliquoting amounts of the solution equivalent to 15 reactions for freeze-drying, therefore, Klatser's batches are aliquots. Finally, Applicant argues that Klatser et al. teach stabilization of enzymes and do not teach stabilization of nucleic acid standards. First, it is not clear what it means to "stabilize a nucleic acid", and Applicant does not claim such stabilization step.

The rejection is maintained.

F) Regarding the rejection of claims 5 and 34 under 35 U.S.C. 103(a) over Day et al., Koehler et al. and Barany et al., Applicant argues that even if the references of Day et al. and Koehler et al. could be combined, the resulting combination would not have the stability properties described by Applicant. However, it is not clear what Applicant means when referring to the nucleic acids produced with "high stability". From the structural point of view, stability of nucleic

acids in solution is irrelevant to the instant claims, since they are drawn to dried nucleic acid, not a nucleic acid in solution. Therefore, properties of nucleic acids in solution have no relationship to the instant claims.

The rejection is maintained.

G) Regarding the rejection of claims 2, 7, 12, 13, 16, 18, 23, 24, 27 and 28 under 35 U.S.C. 103(a) over Klatser et al., Cottingham, Irvine et al. and Longiaru et al., Applicant argues that Cottingham does not teach calibrated standards, Longiaru et al. teach probes which are not desorbable from the well, and Irvine et al. teach dilution standards but not their stabilization.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The references cited above should be considered together as they all provide limitations which make the claims obvious. Applicant does not argue the combination of the references.

The rejection is maintained.

H) Regarding the rejection of claims 5, 10, 21 and 34 under 35 U.S.C. 103(a) over Klatser et al., Koehler et al. and Barany et al., Applicant states that the traverse is based on the argument presented for points 11 and 12. These arguments were addressed above.

The rejection is maintained.

I) Regarding the rejection of claims 9 and 20 under 35 U.S.C. 103(a) over Klatser et al., Koehler et al. and Miyamura et al., Applicant argues that Miyamura et al. has no relationship to the present invention since they do not teach stabilization of standard nucleic acids.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The references cited above should be considered together as they all provide limitations which make the claims obvious. Applicant does not argue the combination of the references.

The rejection is maintained.

Claim Objections

4. Claims 38-44 objected to because of the following informalities:

A) In claim 38, there is no point at the end of the claim and "or" without continuation of the claim.

B) In claim 39, there is no point at the end of the claim.

C) In claim 40, the first step ends in a point and there is no point at the end of the claim.

D) Claim 41 ends with colon and semicolon.

E) Claims 42 ends with a comma.

F) In claim 43, the first step has two commas after "parameter" and steps two and three end with points.

G) In claim 44, the second steps ends with a point and a semicolon. In addition, in the first step the sentence reads "that problem free shipment may is guaranteed". It is not clear which of those two verbs should be considered.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 43 contains, as step four, "mildly drying aliquots of respective standard nucleic acid dilution supplemented by the carrier nucleic acid directly in the reaction chambers used", as step five, "performing lyophilization by means of a vacuum centrifuge or a freeze-drier", as step six, "drying for obtaining a superheating-free product", and as step seven, "drying with the use of microwaves". This sequence of steps constitutes a new matter, since Applicant did not described performing all of the drying steps in such a sequence. On page 9 of the specification (lines 9-11), Applicant lists these drying methods as alternatives, not as steps to be used together.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5, 36-38 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because of the limitation "serve for producing a thinning sequence out of the calibrated nucleic acid". It is not clear what it means to "produce a thinning sequence out of nucleic acid".

9. Claims 36-38 and 43 are rejected as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph.

The claim(s) are narrative in form and replete with indefinite and functional or operational language. The structure which goes to make up the device must be clearly and positively specified. The structure must be organized and correlated in such a manner as to present a complete operative device. The claim(s) must be in one sentence form only.

A) Claim 36 is indefinite over the recitation of "transforming the coated reaction chambers into a form imperishable for prolonged periods of time without impairments of quality". It is not clear what this phrase means. For example, what does it mean "without impairments of quality" as applied to a reaction chamber with dried DNA in it ? Does the term "quality" refer to the DNA, the chamber or to both? Further, it is not clear what "imperishable" means with respect to a reaction chamber with dried DNA in it, or what is meant by "a prolonged period of time".

B) Claim 37 is indefinite over the recitation of "furnishing an automated quantitative measurement of smallest amounts of analyte nucleic acids in diverse biological materials in conjunction with a previous enzymatic amplification". It is not clear at all what this phrase means.

C) Claim 37 is indefinite over the recitation of "transforming nucleic acids into a form appropriate for the standardization of quantitative enzymatic amplification reactions". First, it is not clear which nucleic acid this phrase refers to, since in claim 35 there are standard nucleic acids, calibrated nucleic acids and carrier nucleic acids. Further, it is not clear what the term "a form appropriate for the standardization of quantitative enzymatic amplification reactions" means.

D) Claim 37 is indefinite over the recitation of "wherein the standard nucleic acids are single-stranded or double-stranded DNA or RNA or synthetic equivalents of DNA and RNA, as well as DNA, the native deoxythymidine (dT) bases thereof being completely or partially

substituted by deoxyuracil (dU)". It is not clear of whether all of the nucleic acids listed in the claim should have the dTs substituted with dUs.

E) Claim 38 is indefinite over the recitation of "primer or probe bonding point". It is not clear what a "bonding point" is with reference to a nucleic acid.

F) Claim 43 is indefinite over the recitation of "quantification of a measurement parameter". It is not clear what the "measurement parameter" is.

G) Claim 43 is indefinite over the recitation of "wherein the enzymatic nucleic acid amplifications necessary for the establishment of an calibration graph, are to take place". It is not clear what this limitation means. If it is supposed to mean an amplification step, an active step should be added to the claim.

H) Claim 43 is indefinite over the recitation of "mildly drying", since it is not clear what characterizes "mild" drying.

I) Claim 43 is indefinte over the sequence of the drying steps, since it is not clear whether all of these steps were to be performed together or as alternative drying steps, as indicated by the specification.

Applicant is notified that the best effort is made to interpret the above claims for the purpose of art rejections.

Claim Interpretation

10. The term "reaction chamber" is interpreted as any container.

11. The terms "calibrated nucleic acid", "carrier nucleic acid" and "standard nucleic acid" are interpreted as any nucleic acid, since they were not defined in the specification.

12. For the purpose of art rejection, the drying steps of claim 43 are interpreted as alternative drying steps, since this is suggested by the specification, and from the practical point of view it would not make any sense to perform all of them on the same sample.

13. The following rejection is based on the product claimed in claims 1, 29 and 30, which is "Reaction chambers coated with native, synthetically or enzymatically prepared nucleic acids", irrespective of the way in which they were obtianed (see MPEP 2113 and 2114). Further, the limitations "storable without problems for a prolonged period of time with unchanged quality" (claim 1) and "suitable to be stored at room temperature for a period longer than a year without loss of quality" (claim 29) refer to the properties of the reaction chambers, not their structural limitations. The limitations "useable for kits" (claim 2), use of dilution solutions (claims 4 and 33) are intended use limitations, which, again, do not impose structural constraints on the product (see MPEP 2114).

MPEP 2113 Product-by-Process Claims

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

MPEP-2114 [R-1] Apparatus and Article Claims — Functional Language

APPARATUS CLAIMS MUST BE STRUCTURALLY DISTINGUISHABLE FROM THE PRIOR ART

>While features of an apparatus may be recited either structurally or functionally, claims< directed to >an< apparatus must be distinguished from the prior art in terms of structure rather than function. >In re Schreiber, 128 F.3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997) (The absence of a disclosure in a prior art reference relating to function did not defeat the Board's finding of anticipation of claimed apparatus because the limitations at issue were found to be inherent in the prior art reference); see also In re Swinehart, 439 F.2d 210, 212-13, 169 USPQ 226, 228-29 (CCPA 1971);< In re Danly, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original).

MANNER OF OPERATING THE DEVICE DOES NOT DIFFERENTIATE APPARATUS CLAIM FROM THE PRIOR ART

A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987)

MPEP 2114.

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A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987) (The preamble of claim 1 recited that the apparatus was "for mixing flowing developer material" and the body of the claim recited "means for mixing ..., said mixing means being stationary and completely submerged in the developer material". The claim was rejected over a reference which taught all the structural limitations of the claim for the intended use of mixing flowing developer. However, the mixer was only partially submerged in the developer material. The Board held that the amount of submersion is immaterial to the structure of the mixer and thus the claim was properly rejected.).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-4, 29 and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Day et al. (Biotechniques, vol. 18, pp. 981-984, 1995; cited in the previous office action).

Day et al. teach 96-well plates coated with DNA templates which were dried in the wells. The plates can then be used for setting up PCR reactions. Alternatively, PCR primers are distributed into the wells and dried there. In both cases, adherence of the dried DNA to the walls of the wells is non-covalent, since both dried template and dried primers function in subsequent PCR reactions (page 381-383).

15. Claims 1, 3, 4, 6, 8, 11, 14, 15, 17, 19, 22, 25, 26, 29, 30, 32, 33 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998).

Regarding claims 1, 3, 4, 29, 30, 32 and 33, Klatser et al. teach containers with DNA primers which were non-covalently adsorbed onto the surface by freeze-drying (page 1798, third paragraph; page 1799, second paragraph).

Regarding claims 6 and 17, Klatser et al. teach a method for the production of reaction chambers, the method comprising

directly aliquoting calibrated standard nucleic acids and added carrier nucleic acid into reaction chambers and subsequently non-covalently adsorbing the calibrated standard nucleic acids and added carrier nucleic acids directly in the inner wall of the reaction chamber by means of freeze-drying or vacuum-centrifugating lyophilization (Klatser et al. teach directly adsorbing DNA primers onto container walls by lyophilization of batches of PCR mixes, comprising PCR primers (page 1798, third paragraph). Klatser et al. do not specifically teach a container, but since the samples were lyophilized, they had to be placed in a container, therefore, inherently, Klatser et al. teach the limitations of these claims).).

Regarding claims 8 and 19, Klatser et al. teach using DNA primers (page 1798, third paragraph).

Regarding claims 11 and 22, Klatser et al. teach primers for detection of two different Mycobacterium tuberculosis genes, IS6110 and 16S rRNA (page 1798, second paragraph).

Regarding claims 14 and 25, Klatser et al. teach lyophilizating PCR reaction mix comprising primers, DNA polymerase, dNTPs and uracil-DNA-glycosylase (page 1798, third paragraph).

Regarding claims 14, 25 and 45, Klatser et al. teach forming a composition for PCR, comprising primers, DNA polymerae, dNTPs, buffer, dUTP and uracil-DNA glycosylase (page 1798, third paragraph).

Regarding claim 15, Klatser et al. teach forming a kit for the detection of Mycobacterium tuberculosis (page 1799, second paragraph).

Claim Rejections - 35 USC § 103

16. Claims 5 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Day et al. (Biotechniques, vol. 18, pp. 981-984, 1995; cited in the previous office action), Koehler et al. (Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and Barany et al. (U.S. patent No. 5,494,810; cited in the previous office action).

A) Day et al. do not teach carrier nucleic acid being λ DNA.

B) Koehler et al. teach addition of λ DNA digested with HindIII as a carrier to stabilize standard DNA in solution (page 724, second paragraph; page 725, second paragraph). Koehler et al. do not teach sonicated λ DNA.

C) Barany et al. teach using sonicated salmon sperm DNA as a carrier (col. 34, lines 29, 30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used λ DNA as a carrier in the formation of plates of Day et al. The motivation to

do so, provided by Koehler et al., would have been that presence of carrier DNA stabilized DNA in dilute solution and prevented non-specific binding of DNA to the tubes (page 724, second paragraph) and diminished variability in the amplification reactions using the competitor in solution (page 725, second paragraph). The motivation to sonicate the λ DNA of Koehler et al., provided by Barany et al., would have been that the sonicated DNA provided no background in amplification reactions (col. 36, lines 21-23).

17. Claims 2, 7, 12, 13, 16, 18, 23, 24, 27, 28, 44 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998; cited in the previous office action), Cottingham (U.S. Patent No. 5,948,673; cited in the previous office action), Irvine et al. (U.S. Patent No. 6,300,056; cited in the previous office action) and Longiaru et al. (EP 0 420 260 A2; cited in the previous office action).

A) Klatser et al. teach lyophilization of PCR reaction mixes, but do not specifically teach plastic or glass containers, 96 reaction chambers or different concentrations of aliquoted nucleic acids.

B) Regarding claims 2, 7 and 18, Cottingham teaches a DNA card comprising dried nucleic acid amplification reagents in the wells of sample chambers which are formed from plastic (col. 3, lines 45-48; col. 7, lines 55-64).

Regarding claims 12, 16, 23, 27, 28, 44 and 46, Cottingham teaches a DNA card comprising 64 identical sample cells, arranged in eigth rows and eight columns (col. 6, lines 19-25). The wells are sealed with a flexible, pressure sensitive material (col. 4, lines 5-10). The sealing strips cover one octet strip of the plate, to define segments which can be used individually (col. 6, lines 27-40).

C) Cottingham does not teach 96 reaction chambers or different concentrations of aliquoted nucleic acids.

D) Regarding claims 12, 13, 16, 23, 27, 28 and 44, Longiaru et al. teach preparation of microplates with capture probes for quantitation of amplification reaction products. The known amounts (25 ng) of probes are non-covalently bound to the wells of either a 96-well plate or to strips of 12 tubes which fit into strip holders in a microtiter plate format, and the plates are sealed (page 6, lines 26-46).

E) Longiaru et al. do not teach different concentrations of probes.

F) Irvine et al. teach quantitation of HIV DNA by amplification of sample containing the HIV DNA on a microplate, the wells of which contain known amounts of HIV DNA in the range of 10 to 200 tmoles (1 tmole = 602 molecules), and preparing standard curve of the DNA concentration (col. 13, lines 17-50).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used multiple reaction chambers, such as wells on a microplate of Longiaru et al., and multiple concentrations of nucleic acid of Irvine et al., in the method of formation of reaction chambers of Klatser et al. The motivation to do so, provided by Cottingham, would have been that multiple well format can be conveniently handled by clinical personnel and all reagents for both DNA amplification and detection are provided within the device (col. 2, lines 45-49, 55-61). The motivation to do so, provided by Irvine et al., would have been that having a set of standard nucleic acids provided means for determining the concentration of HIV DNA down to 50 tmoles (= about 30,000 molecules) (col. 14, lines 5-17).

18. Claims 5, 10, 21 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action), Koehler et al. (Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the

previous office action) and Barany et al. (U.S. patent No. 5,494,810; cited in the previous office action).

A) Klatser et al. do not teach carrier nucleic acid being λ DNA.

B) Koehler et al. teach addition of λ DNA digested with HindIII as a carrier to stabilize standard DNA in solution (page 724, second paragraph; page 725, second paragraph). Koehler et al. do not teach sonicated λ DNA.

C) Barany et al. teach using sonicated salmon sperm DNA as a carrier (col. 34, lines 29, 30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used λ DNA as a carrier in the formation of plates of Klatser et al. The motivation to do so, provided by Koehler et al., would have been that presence of carrier DNA stabilized DNA in dilute solution and prevented non-specific binding of DNA to the tubes (page 724, second paragraph) and diminished variability in the amplification reactions using the competitor in solution (page 725, second paragraph). The motivation to sonicate the λ DNA of Koehler et al., provided by Barany et al., would have been that the sonicated DNA provided no background in amplification reactions (col. 36, lines 21-23).

19. Claims 9 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action), Koehler et al. (Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and Miyamura et al. (U.S. Patent No. 5,747,241; cited in the previous office action).

A) Klatser et al. do not teach dilution of DNA standards using a DNA solution having a minimum sequence homology to the nucleic acid being analyzed, or dilution of RNA standards using tRNA solution.

B) Koehler et al. teach addition of λ DNA digested with HindIII as a carrier to stabilize standard DNA in solution (page 724, second paragraph; page 725, second paragraph). Koehler et al. do not teach using tRNA.

C) Miyamura et al. teach adding tRNA to a serum sample which contains HCV RNA (col. 2, lines 63-67; col. 3, lines 1-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used λ DNA of Koehler et al. as a carrier in the formation of plates of Klatser et al. The motivation to do so, provided by Koehler et al., would have been that presence of carrier DNA stabilized DNA in dilute solution and prevented non-specific binding of DNA to the tubes (page 724, second paragraph) and diminished variability in the amplification reactions using the competitor in solution (page 725, second paragraph). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used tRNA of Miyamura et al. as a carrier in the formation of plates of Klatser et al. The motivation to do so, provided by Miyamura et al., would have been that the presence of tRNA was advantageous because it provided an indicator of RNA degradation (col. 3, lines 4-9).

20. Claims 35-39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohler et al. ((Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action).

Regarding claim 35, Kohler et al. teach preparation of nucleic acid standards for quantitative amplification by the method comprising:

preparing an adsorbable standard nucleic acid (Kohler et al. teach praparation of standard nucleic acid by PCR amplification of cDNA (page 722, last paragraph). Since every nucleic acid can be adsorbed onto something. Kohler et al. inherently teach this limitation.);

purifying the adsorbable standard nucleic acid (Kohler et al. teach purification of the standard nucleic acid (page 723, first paragraph).);

determining a precise concentration of the adsorbable standard nucleic acid by means of high performance liquid chromatography (HPLC) thereby furnishing a calibrated nucleic acid (Kohler et al. teach determination of the nucleic acid concentration by HPLC (page 723, second paragraph; Fig. 1).);

preparing a dilution member from the calibrated nucleic acid with an addition of defined quantities of a carrier nucleic acid (Kohler et al. teach preparing dilutions of the standard nucleic acid (page 724, second paragraph; Fig. 2).);

employing a chamber (Kohler et al. teach storage tubes (= chambers) (page 724, second paragraph).);

directly aliquoting the dilution member into the chamber (Kohler et al. teach aliquoting the dilutions into the tubes (page 724, third paragraph).).

Regarding claim 36, Kohler et al. teach using the dilutions as DNA standards (page 723, fourth paragraph; page 724, first and third paragraphs; Fig. 2).

Regarding claim 37, Kohler et al. teach making dilutions of the standard nucleic acid (= transforming nucleic acids into a form appropriate for the standardization of quantitative enzymatic amplification reactions) (page 724, second paragraph; Fig. 2), the nucleic acid being double-stranded DNA and standard nucleic acid preparation by PCR (page 722, last paragraph).

Regarding claim 38, Kohler et al. teach preparing the standard nucleic acid by PCR (page 722, last paragraph) and the standard being 88 bp shorter than the target (page 724, second paragraph).

Regarding claim 39, Kohler et al. teach preparing the standard nucleic acid by PCR (page 722, last paragraph) and DNA purification by agarose gel electrophoresis (page 723, first paragraph).

Regarding claim 42, Kohler et al. teach using unmodified lambda DNA for dilution of the DNA standards (page 724, second paragraph).

B) Kohler et al. do not teach lyophilizing the aliquoted nucleic acids by freeze-drying and non-covalently adsorbing the nucleic acids onto an inner wall of the chamber.

C) Regarding claims 35 and 37, Klatser et al. teach directly adsorbing DNA primers onto container walls by lyophilization of batches of PCR mixes, comprising PCR primers (page 1798, third paragraph). Klatser et al. do not specifically teach a container, but since the samples were lyophilized, they had to be placed in a container, therefore, inherently, Klatser et al. teach the limitation of a reaction chamber. Klatser et al. teach ready to use reaction chambers which are storable without problems for a prolonged period of time and which may be used as components for test kits (page 1799, last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the lyophilization method of Klatser et al. to prepare nucleic acid standards of Kohler et al. The motivation to do so, provided by Klatser et al., would have been that lyophilized standards were stable at 20° C for a year and at 37° C for up to 3 months (page 1799, last paragraph).

21. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kohler et al. ((Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and

Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action), as applied to claim 35 above, and further in view of Zimmerman et al. (BioTechniques, vol. 21, pp. 268-279, 1996; cited in the IDS).

A) Regarding claim 40, Koehler et al. teach measuring concentration of nucleic acids by HPLC (page 273, first paragraph). Neither Koehler et al. nor Klatser et al. teach RNA fragments prepared by in vitro RNA synthesis.

B) Zimmerman et al. teach preparation of RNA standards by in vitro transcription using RNA polymerase, purification of the RNA and extraction (page 52, fourth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the RNA standards of Zimmerman et al. in the method of Koehler et al. nor Klatser et al. The motivation to do so, provided by Zimmerman et al., would have been that the RNA standards are used for precise quantitation of RNA in competitive RT-PCr (page 268, second and last paragraphs; page 269, first paragraph).

22. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koehler et al. (Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action), as applied to claim 35 above, and further in view of Barany et al. (U.S. patent No. 5,494,810; cited in the previous office action).

A) Koehler et al. teach addition of λ DNA digested with HindIII as a carrier to stabilize standard DNA in solution (page 724, second paragraph; page 725, second paragraph). Koehler et al. do not teach sonicated λ DNA.

C) Barany et al. teach using sonicated salmon sperm DNA as a carrier (col. 34, lines 29, 30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used λ DNA as a carrier in the formation of plates of Koehler et al. and Klatser et al. The motivation to do so, provided by Koehler et al., would have been that presence of carrier DNA stabilized DNA in dilute solution and prevented non-specific binding of DNA to the tubes (page 724, second paragraph) and diminished variability in the amplification reactions using the competitor in solution (page 725, second paragraph). The motivation to sonicate the λ DNA of Koehler et al., provided by Barany et al., would have been that the sonicated DNA provided no background in amplification reactions (col. 36, lines 21-23).

23. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koehler et al. (Biotechniques, vol. 23, pp. 722-726, 1997; cited in the IDS and in the previous office action) and Klatser et al. (J. Clin. Microbiol., vol. 36, pp. 1798-1800, June 1998 ; cited in the previous office action), as applied to claim 35 above, and further in view of Cottingham (U.S. Patent No. 5,948,673; cited in the previous office action).

A) Regarding claim 43, Kohler et al. teach preparations of dilutions for measurement of initial MRP cDNA concentrations (page 724, last paragraph; page 725, first paragraph; Fig. 2). Regarding claim 43, Klatser et al. teach directly adsorbing DNA onto container walls by lyophilization of batches of PCR mixes, comprising PCR primers (page 1798, third paragraph).

B) Neither Kohler et al. nor Klatser et al. teach preparing eight separate reaction chambers.

C) Cottingham teaches a DNA card comprising 64 identical sample cells, arranged in eigth rows and eight columns (col. 6, lines 19-25). The wells are sealed with a flexible, pressure sensitive material (col. 4, lines 5-10). The sealing strips cover one octet strip of the plate, to define segments which can be used individually (col. 6, lines 27-40).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the octet strips of Cottingham in the method of Kohler et al. nor Klatser et al. The motivation to do so, provided by Cottingham, would have been that the card format was conveniently handled by clinical laboratory personnel and accommodated in a suitable test apparatus (col. 2, lines 45-49).

24. No claims are allowed.

Conclusion

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
December 2, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER
12/3/04